II. REMARKS

Formal Matters

Claims 1-12 and 25-27 are pending after entry of the amendments set forth herein.

Claims 1-12 and 25-27 were examined and were rejected.

Claim 1 is amended. The amendments to claim 1 were made solely in the interest of expediting prosecution, and are not to be construed as an acquiescence to any objection or rejection of any claim. Support for the amendments to claim 1 is found in the claims as originally filed, and throughout the specification, in particular at the following exemplary location: page 5, lines 20-24. Accordingly, no new matter is added by these amendments.

Please replace claim 1 with the clean version provided above.

Attached hereto is a marked-up version of the changes made to claim 1 by the current amendment. The attached is captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE.**"

Applicants respectfully request reconsideration of the application in view of the remarks made herein.

Rejection under 35 U.S.C.§112, first paragraph

The Office Action stated that claims 1-12 and 17-24 are rejected under 35 U.S.C.§112, first paragraph, on the basis that the specification is allegedly not enabling for the full scope of the claims. However, claims 17-24 are not currently pending. Applicants presume that the Office Action intended to state that claims 1-12 and 25-27 are rejected under 35 U.S.C.§112, first paragraph, and will respond accordingly.

The Office Action stated that the specification does not provide enablement of a method of detecting an increased susceptibility to bipolar mood disorder (BP) by detecting polymorphisms between and inclusive of SAVA5 and ga203 or any of the other recited markers wherein the presence of a disease chromosome indicates an increased susceptibility to BP. Applicants respectfully traverse the rejection.

The specification provides ample description of polymorphisms associated with BP, and further provides a detailed description of how to determine whether a given polymorphism is associated with BP.

Applicants have described in great detail:

(1) Identification of a narrow interval, between markers SAVA5 and ga203, on the short arm of chromosome 18 which contains polymorphisms associated with BP. This identification was achieved by performing an analysis on a genetically isolated population, as described in detail in the specification. Specification, page 16, line 12 to page 25, line 10.

(2) Identification of polymorphisms, e.g., allele 154 at D18S59, a microsatellite marker polymorphism that associates with BP; and allele 271 at D18S476, another microsatellite marker polymorphism that associates with BP. Specification, page 24, lines 10-29. Thus, at least two polymorphisms are unequivocally associated with BP.

(3) How additional polymorphisms within the defined, narrow region can be identified in other BP patients. Specification, page 27, line 22 to page 29, line 29.

(4) How individuals whose BP status is unknown ("test individuals") can be analyzed for the presence of a polymorphism known to be associated with BP. Specification, page 29, lines 23-29.

The Office Action stated that the specification is enabling for a method of detecting an increased susceptibility for bipolar mood disorder by performing a pedigree analysis for the individual's family, and analyzing the DNA from family members for linkage of markers on the short arm of chromosome 18 between and inclusive of SAVA5 and ga203, D18S1140 and ga203, SAVA5 and W3422, D18S1140 and W3422, D18S1140 and ta201, and D18S59 and ta201.

However, as shown in the Examples, Applicants demonstrated unequivocally that at least two polymorphisms, e.g., allele 154 at D18S59, a microsatellite marker polymorphism that associates with BP; and allele 271 at D18S476, are associated with BP in *both pedigree analysis and in an analysis of a population of unrelated individuals.* Thus, the claims are enabled for performing an analysis on a sample of DNA from a test individual, and need not be limited to performing a pedigree analysis.

The Office Action stated that the specification has not identified polymorphisms in the region between SAVA5 and ga203 that can be detected in any individual and which are generally associated with BP. However, as discussed above, the finding that the above-discussed polymorphisms were identified in a population of unrelated individuals indicates that such polymorphisms are generally associated with BP.

The Office Action further stated that the markers described in the specification are not in an of themselves BP susceptibility polymorphisms because these markers are polymorphic sequences which are found throughout the genome and are not specific to this described region of chromosome 18. This is not correct. While it is true that microsatellite markers in general are found throughout the genome, the specific microsatellite markers identified in the present application are not found throughout the genome. The specific microsatellite markers identified in the instant application, e.g., D18S59 and D18S476, are found only in the narrow region between SAVA5 and ga203, and the specific allele sizes of D18S59 and D18S476 of 154 and 271 bp, respectively, were shown to be associated with BP.

Applicants have described in detail how to identify additional polymorphisms associated with BP.

As noted above, Applicants have described in great detail: (1) Identification of a small interval, between markers SAVA5 and ga203, on the short arm of chromosome 18 which contains polymorphisms associated with BP, which identification was achieved by performing an analysis on a genetically isolated population, as described in detail in the specification; (2) Identification of polymorphisms, e.g., allele 154 at D18S59, and allele 271 at D18S476, which associate with BP (see, e.g., Table I, page 24); and (3) How additional polymorphisms within the narrow interval can be identified in other BP patients. Those skilled in the art can thus identify, using the guidance in the specification, a polymorphism(s) within the identified region that associate with BP. The specification provides both a narrow region that is associated with BP (namely, the region on chromosome 18 between SAVA5 and ga203) as well as polymorphisms within this region that associate with BP. Thus, the specification is indeed enabling for a method of detecting the presence of a BP susceptibility polymorphism in an individual.

Given the guidance provided in the specification, those skilled in the art could readily determine whether a given polymorphism within the region recited in the claims is associated with BP. The Declaration of Alison McInnes, provided herewith as Exhibit 1, attests to this fact. The Declaration shows that, using techniques described in the specification, at least five new polymorphisms, including single nucleotide polymorphisms (SNP), were identified in the narrow interval on chromosome 18p described in the application, which polymorphisms are associated with BP. Thus, in addition to the polymorphisms already identified in the patent application, and using the guidance provided in the application, several additional polymorphisms were identified that are associated with BP.

The cited art does not support a conclusion of non-enablement of the instant claims.

The Office Action cited various publications in support of the contention that the teachings in the specification do not provide the skilled artisan with a reasonable expectation that he will identify polymorphisms that are associated with bipolar mood disorder or for detecting a bipolar (BP) susceptibility locus without undue experimentation because of the extensive amount of unpredictability in this field. The cited art are Stine et al. ((1995) *Am. J. Hum. Genet.* 57:1384-1394); McInnes et al. ((1996) *Proc. Natl. Acad. Sci.* 93:13060-13065;); Esterling et al. ((1997) *Molec. Psychiatry* 2:501-504); Ewald et al. ((1997) *Psychiatric Genetics* 7:1-12); Gershon et al. ((1998) *Neuropsychopharmacology* 18:233-242); and Nöthen et al. ((1999) *Molec. Psychiatry* 4:76-84"). Applicants respectfully traverse the rejection.

The present invention is based on studies that differed from previous studies in several respects. These differences can account for the failure of others, and the success of the present inventors, in finding polymorphisms associated with BP. These difference include: (1) others reported **pedigree-based studies**, while the present invention relates to a **population-based study**; (2) others did not use **linkage disequilibrium analysis**; and (3) others **included irrelevant phenotypes**, while the present study **excluded irrelevant phenotypes**. These differences were described in detail in the response to the June 28, 2000 Office Action. *Since the cited studies could not have provided the kind of information that the instant inventors were able to provide, none of the cited art supports a conclusion of non-enablement of the instant claims.*

Applicants submit that the rejection of claims 1-17 and 25-27 under 35 U.S.C. §112, first paragraph, has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

Rejection under 35 U.S.C.§112, first paragraph

The Office Action stated that claims 1-12 and 17-24 are rejected under 35 U.S.C.§112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. However, claims 17-24 are not currently pending. Applicants presume that the Office Action intended to state that claims 1-12 and 25-27 are rejected under 35

U.S.C.§112, first paragraph, and will respond accordingly. Applicants respectfully traverse the rejection as it might be applied to claims 1-12 and 25-27.

The Office Action stated that the specification has not provided a written description of a representative number of species of polymorphisms associated with BP. The Office Action went on to state that the specification "only teaches several" specific allele sizes that are associated with bipolar mood disorder. "Several" specific allele sizes would appear to satisfy the "representative number" requirement.

The Office Action further stated that a polymorphism includes point mutations, small deletions, insertions, none of which have been described in the specification. However, *there is no statutory requirement that Applicants describe all types of polymorphisms*. Furthermore, it is not necessary to provide detailed sequence information for every type of polymorphism. Many polymorphisms can be identified and detected without the need to determine the nucleotide sequence. For example, microsatellite polymorphisms and other types of polymorphisms can be detected without sequencing. Thus, while polymorphisms encompass all types of polymorphisms, including point mutations, deletions, insertions, etc., sequencing of such polymorphisms is not required in order to carry out the claimed invention.

The Office Action further stated that there are so many genetic variations which are inherited from family members that would have no association with BP. However, the claims recite that the polymorphism is one that is associated with BP. Thus, if the polymorphism is not associated with BP, it is excluded.

Applicants submit that the rejection of claims 1-17 and 25-27 under 35 U.S.C. §, first paragraph, has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

Rejection under 35 U.S.C.§112, second paragraph

Claims 1-12 and 25-27 were rejected under 35 U.S.C.§112, second paragraph, as allegedly indefinite.

The Office Action stated that claims 1-12 and 25-27 are indefinite over the recitation of "a disease chromosome." Applicants respectfully traverse the rejection.

Applicants note that claims 9 and 10 do not recite "a disease chromosome." Accordingly, the rejection does not apply to claims 9 and 10.

The Examples describe polymorphisms associated with BP. From the description in the Examples, it is clear that a "disease chromosome" is a chromosome bearing a polymorphism (e.g., a microsatellite allele) associated with BP. See, e.g., specification, page 21, line 1 to page 25, line 10. Thus, the term "a disease chromosome" is clear, and the claims need not be amended.

Applicants submit that the rejection of claims 1-17 and 25-27 under 35 U.S.C. §112, second paragraph, has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

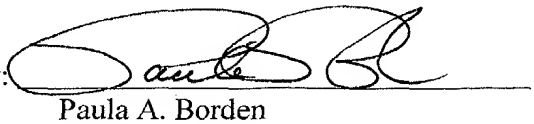
III. CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number UCAL142CON.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: Oct. 10, 2001

By: 
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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Please enter the amendment to claim 1, as shown below.

1. (Twice Amended) A method of detecting an increased susceptibility to bipolar mood disorder (BP) in an individual comprising:

analyzing a sample of DNA from a test individual for the presence of a DNA polymorphism associated with BP on the short arm of chromosome 18 between SAVA5 and ga203, wherein the presence in the test individual of a polymorphism associated with BP which is present on a disease chromosome indicates that the test individual has an increased susceptibility to develop BP.